Autonomic dysfunction in cardiovascular disease

Lefrandt, Johan Daniël

Part III: Hypertension

Chapter 6

Autonomic Function in Hypertensive and Normotensive Subjects

The Importance of Gender

Hypertension. 2001 June;37:1351–6

K. Sevre[1], J. D. Lefrandt[4], G. Nordby[2], I. Os[2], M. Mulder[4], R. O.B. Gans[4], M. Rostrup[2,3], A. J. Smit[4].

Departments of Cardiology[1], Internal Medicine[2], and Research Forum[3], Ullevål University Hospital, Oslo, Norway;

Department of Internal Medicine[4], University Hospital of Groningen, The Netherlands.

Summary

Baroreceptor reflex sensitivity (BRS) has been found lower and heart rate variability (HRV) parasympathetic markers have been found higher in healthy women than in healthy men. Thus, in the present study we hypothesized gender differences in the autonomic function among hypertensive subjects. Forty–one hypertensive patients and 34 normotensive subjects, age 53 ± 1 years, were examined. Four weeks after cessation of antihypertensive therapy, HRV was assessed in 24–hour Holter ECGs, and BRS was calculated with the transfer technique. A *t* test was performed after log transformation of spectral values. Resting blood pressure and heart rate in the hypertensive and the normotensive groups were 150 ± 2/100 ± 1 (mean ± SEM) and 121 ± 2/81 ± 1 mmHg, respectively, and 68 ± 1 and 60 ± 1 bpm, respectively ($P<0.0005$). Compared with normotensive controls, hypertensive patients had lower total power (1224 ± 116 versus 1797 ± 241 ms^2; $P=0.03$), lower low frequency power (550 ± 57 versus 813 ± 115 ms^2; $P=0.04$), lower high frequency power (141 ± 23 versus 215 ± 38 ms^2; $P=0.06$), lower root mean square successive difference (28.7 ± 2.7 versus 35.7 ± 3.0 ms; $P=0.03$), and PNN50 (4.9 ± 0.6% versus 9.8 ± 1.5%; $P=0.003$). BRS was also lower in the hypertensive subjects (7.6 ± 0.6 versus 10.4 ± 0.8 ms/mmHg; $P=0.005$). When comparing the same parameters between normotensive subjects and hypertensive subjects within the same gender group, we found significant reduction ($P<0.05$) only within the female group. The difference in BRS within the female group was twice that within the male group. Stepwise multiple regression analysis revealed gender, age, HDL cholesterol, and blood pressure as independent explanatory variables of BRS and HRV. Our results suggest that gender is an important determinant of BRS and HRV. Autonomic function parameters were especially impaired in hypertensive women compared with hypertensive men.

Introduction

The autonomic nervous system plays a crucial role in blood pressure (BP) and heart rate (HR) control and may thus be an important pathophysiological factor in the development of hypertension. There have been numerous studies on plasma catecholamines in essential hypertension,[1] most of which have shown increased levels in hypertensive subjects. Moreover, disturbed autonomic HR and BP control has been demonstrated in several studies by means of HR variability (HRV) and baroreceptor reflex sensitivity (BRS).[2–10]

HRV, which estimates the tonic HR control,[11–13] is generally reduced (standard deviation of all R–R intervals [SDNN] and total power [energy in the heart period spectrum between 0.0033 and 0.40 Hz] [TP]) in hypertensive patients.[2,4–6] Markers of sympathetic predominance are increased in some[3] but not all studies.[4–6]

BRS, which estimates the reflex vagal HR control,[11–13] is reduced in hypertensive subjects.[6–10] Both BRS and HRV parameters (except low frequency power [energy in the heart period spectrum between 0.04 and 0.15 Hz] [LF]/high frequency power [energy in the heart period spectrum between 0.15 and 0.40 Hz] [HF]) decrease with increasing age in healthy[10,14] and hypertensive subjects.[10] It is also proposed that BRS stabilizes after middle age.[8]

There may be gender differences in the pathophysiology of essential hypertension. We have previously observed that hypertensive women have low–renin hypertension[15] and less cardiovascular reactivity to stress compared with hypertensive men.[16] However, thus far there has been only 1 specific study on possible gender differences in HRV in hypertension,[4] and there have been none on BRS. Singh et al[4] found reduced LF/HF ratio but not TP, percentage of adjacent R–R intervals differing >50 ms (PNN50), square root of the mean of the sum of the squares of differences between adjacent R–R intervals (RMSSD), LF, and HF in hypertensive women compared with hypertensive men.

However, there are more studies on gender differences in healthy subjects. SDNN,[4,17,18] LF/HF ratio, and LF normalized units [LF/(LF+HF)×100][4,17,19] have been found lower and HF normalized units [HF/(LF+HF)×100][17] and HF[4,17,19] have been found higher in women than in men. Moreover, BRS is reduced in women compared with men,[14,17,18,20] but the difference is not significant in those age ≥60 years.[14]

In both healthy and hypertensive subjects, previous studies suggest a higher tonic parasympathetic activity in women than in men. Surprisingly, these studies also propose decreased reflex vagal responses in healthy women compared with healthy men. However, the correlation between HRV and BRS is weak.[12]

While gender differences in HRV and BRS have been studied in healthy subjects, no one has addressed specifically gender differences in BRS in hypertensive patients compared with normotensive controls. This article presents some new findings suggesting that autonomic dysfunction may play a more prominent role in female than in male hypertension.

METHODS

Subjects. Patients were eligible if they were age >18 years and suffered from mild to moderate hypertension (systolic BP≥140 and ≤180 mmHg, diastolic BP≥90 mmHg). Patients were excluded if secondary hypertension was suspected, if they had recently suffered from a cardiovascular event, if organ failure was present, or if they had diabetes mellitus, autoimmune disease, or Parkinson's disease. Use of neuroleptics, antidepressants, lithium, antiarrhythmics, and cimetidine was not allowed. These criteria were similar for the normotensive controls except for their BP level, which had to be <140/90 mmHg.

Patients were recruited from the outpatient clinic for hypertensive patients, Ullevål University Hospital, Oslo, Norway, and the University Hospital of Groningen, Netherlands. Normotensive controls were partly former participants in a screening program for cardiovascular

Table 1. Basal Characteristics in Normotensive vs Hypertensive Subjects

Basal Parameters	Normotensive	Hypertensive	*P*
n	34	41	
Age, y	52.7 ± 1.5	52.1 ± 1.4	NS
BMI, kg/m^2	26.5 ± 0.6	26.9 ± 0.5	NS
Smoker, %	23.5	26.8	NS
Hematocrit, fraction	0.40 ± 0.005	0.41 ± 0.006	NS
Creatinine, μmol/L	84.0 ± 2.4	81.0 ± 2.1	NS
Total cholesterol, mmol/L	5.8 ± 0.8	5.6 ± 0.3	NS
HDL cholesterol, mmol/L	1.2 ± 0.06	1.5 ± 0.09	0.02
Triglyceride, mmol/L	1.2 ± 0.1	1.3 ± 0.2	NS
Systolic BP, mmHg	121 ± 2	150 ± 2	<0.0005
Diastolic BP, mmHg	81 ± 1	100 ± 1	<0.0005
HR, bpm	60 ± 1	68 ± 1	<0.0005

Data are mean ± SEM.

Table 2. Basal Characteristics in Normotensive Women vs Hypertensive Women and Normotensive Men vs Hypertensive Men

	Female			Male		
Basal Parameters	Normotensive	Hypertensive	P	Normotensive	Hypertensive	P
n	15	17		19	24	
Age, y	51.4 ± 1.2	54.6 ± 1.5	NS	53.6 ± 2.6	50.3 ± 2.1	NS
BMI, kg/m^2	26.6 ± 1.1	28.3 ± 0.9	NS	26.4 ± 0.6	25.9 ± 0.6	NS
Smoker, %	33.3	11.8	NS	15.8	37.5	NS
Hematocrit, fraction	0.38 ± 0.008	0.39 ± 0.008	NS	0.42 ± 0.005	0.43 ± 0.005	NS
Creatinine, μmol/L	74.1 ± 2.3	70.8 ± 2.2	NS	91.9 ± 2.9	88.5 ± 2.2	NS
Total cholesterol, mmol/L	5.7 ± 0.3	6.0 ± 0.5	NS	5.8 ± 0.3	5.2 ± 0.3	NS
HDL cholesterol, mmol/L	1.5 ± 0.08	1.6 ± 0.2	NS	1.1 ± 0.07	1.4 ± 0.09	0.004
Triglyceride, μmol/L	1.1 ± 0.2	1.4 ± 0.3	NS	1.2 ± 0.1	1.3 ± 0.3	NS
Systolic BP, mmHg	121 ± 2	149 ± 2	<0.0005	121 ± 2	151 ± 3	<0.0005
Diastolic BP, mmHg	81 ± 1	99 ± 1	<0.0005	81 ± 1	100 ± 1	<0.0005
HR, bpm	60 ± 1	69 ± 2	0.009	60 ± 1	67 ± 2	<0.0005

Data are mean ± SEM.
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risk factors. The subjects entered the study between September 1996 and February 1999. All patients gave written informed consent. The regional ethical research committees in both countries approved the protocol. Baseline characteristics at inclusion are summarized in Tables 1 and 2.

Study Procedure. All subjects were examined at 2 visits. At the first visit, patients were advised to stop taking any antihypertensive drugs. The patients who terminated antihypertensive medication were scheduled for BP control once a week after the first visit. At 4 weeks after the first visit, the second visit, the final assessment of eligibility, was performed.

All examinations were performed in the morning in a quiet room with temperature 22°C to 24°C. The subjects were examined after an overnight fast and had refrained from alcohol and tobacco for at least the last 24 hours. HR and sitting sphygmomanometric BP were measured after 10 minutes of rest. Beat–to–beat BP and HR were recorded with the patient in the supine position with a Finapres (Ohmeda 2300) noninvasive BP monitor with the appropriate cuff applied to the third finger of the left hand. This instrument has been validated, and the accuracy and precision have been found sufficient for tracking of changes in BP and HR.[21] A 24–hour Holter ECG was applied to the chest (Marquette series 8500).

Because mental stress can influence autonomic functions, the purpose of visit 1 was to familiarize the patient with the study procedure. Thus, only data from the second visit are presented.

HRV Analysis. Twenty–four– hour ambulatory ECG recordings were analyzed on a Marquette laser Holter system (series 8000XP). HRV was analyzed as described previously[22] and in accordance with international guidelines.[23] Three ECG leads (modified leads V1,V5, and aVF) and a time signal to correct for tape speed irregularities were recorded. The 24–hour recordings were divided into 288 segments of 5 minutes. Twelve 5–minute segments were averaged to obtain hourly mean values of the HRV parameters. All ectopic beats were classified, and only segments with 15% ectopy were used. Each nonnormal R–R interval was substituted by the subsequent R–R interval. Two experienced Holter analysts, with supervision of a cardiologist, analyzed all recordings. Normalized units, TP, LF, and HF have been defined previously in this report.

BRS Measurement. Finapres recordings of 8 segments of 300 seconds of beat–to–beat BP and HR during rest in the supine position were used for determination of the BRS with the CARSPAN program (*Pro*-GAMMA bv), as described previously.[7,24,25] This program allows discrete Fourier transformation of nonequidistant samples of BP and R–R interval series. The signals were tested for stationarity, and artifacts were corrected. Nonstationary signals or periods with >10% correction were excluded. Segments that lasted <100 seconds after this procedure were excluded. Subsequently, spectral analysis of systolic BP and R–R interval length was performed, and BRS was calculated by the transfer function method. This method defines the BRS as the mean modulus between systolic BP and R–R interval length spectra in the midfrequency band (0.07 to 0.14 Hz) with a coherence of >0.5. BRS is expressed in ms/mmHg. A BRS of 10 ms/mmHg indicates that a rise of 1 mmHg in systolic BP will induce 10 ms of R–R interval lengthening.

Statistical Analysis. On the basis of previous studies,[7,9] we expected a possible difference in BRS of 3 ms/mmHg between normotensive and hypertensive subjects. With a possible SD of 3 ms/mmHg, at least 15 patients and 15 controls should be examined with a power of 80%. Because we also planned a subgroup analysis based on gender differences, however, we included more than twice as many subjects in both groups. The data were analyzed with the use of SPSS 9.0.1 statistical package (SPSS Inc). Nonnormal distributed data were natural log trans-

formed. Two–tailed statistical analyses of data were performed with Student's *t* test (*P*) and Pearson's correlation coefficient (*r*). Stepwise multiple regression analysis was performed with gender, BP group (hypertensive or normotensive), age, body mass index (BMI), smoking status, triglyceride, and total and HDL cholesterol as predictors and HRV parameters and BRS as dependent variables. Data are presented as mean ± SEM. The level of statistical significance was set at P=0.05.

Results

Baroreceptor Reflex Sensitivity. All subjects had at least 1 available 300–second period for BRS measurement.

Differences Between Hypertensive and Normotensive Subjects. BRS was reduced in the hypertensive patients compared with the normotensive controls (7.6 ± 0.6 versus 10.4 ± 0.8 ms/mmHg, respectively; P=0.005).

Gender Differences. Hypertensive women had lower BRS than normotensive women. The difference in BRS between male hypertensive and normotensive subjects did not reach statistical significance. Female hypertensive subjects had lower BRS than male hypertensives. BRS did not differ significantly between the 2 normotensive groups (Figure 1). BRS correlated with age in the hypertensive and normotensive male

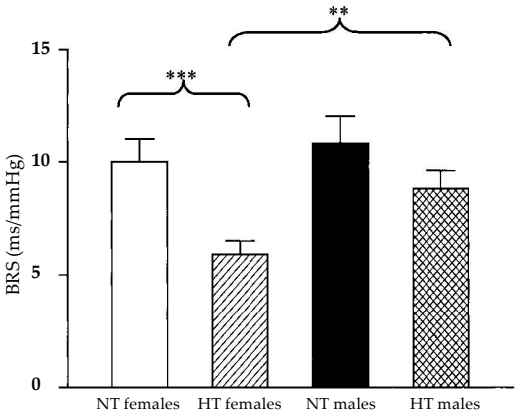

Figure 1. BRS in 41 hypertensive (HT) and 34 normotensive (NT) subjects. BRS was significantly lower in the female hypertensive group than in the female normotensive group but did not differ significantly between the 2 male groups. BRS was significantly lower in the female hypertensive group than in the male hypertensive group but did not differ significantly between the 2 normotensive groups. ***P<0.0005; **P<0.01.

Table 3. Stepwise Multiple Regression With Gender, BP Group, Age, HDL Cholesterol, BMI, Total Cholesterol, Triglyceride, and Smoking Status as Predictors and BRS, Mean R–R, SDNN, PNN50, RMSSD, TP, LF, HF, LF/HF Ratio, LF Normalized Units, and HF Normalized Units as Dependent Variables

	Gender*		HT or NT†		Age		HDL Cholesterol		
Dependent Variables	β	*P*	β	*P*	β	*P*	β	*P*	R^2
BRS, ms/mmHg	–1.8	0.03	–2.9	0.001	–0.3	<0.0005		NS	0.42
Mean R–R, ms	–56.7	0.004	–36.6	0.04		NS	113.4	<0.0005	0.30
SDNN, ms		NS		NS		NS	27.7	0.02	0.08
PNN50, %	–3.2	0.03	–5.0	<0.0005	–0.3	0.001	7.1	<0.0005	0.36
RMSSD, ms	–11.0	0.006		NS		NS	22.5	<0.0005	0.22
TP, ms^2	–897.9	<0.0005	–589.5	0.008	–51.6	<0.0005	842.0	0.006	0.32
LF, ms^2	–360.0	0.001	–279.5	0.009	–28.1	<0.0005		NS	0.35
HF, ms^2	–91.6	0.04		NS	–5.3	0.03	189.7	0.001	0.15
LF/HF ratio		NS		NS	–0.01	0.01	–3.2	<0.0005	0.31
LF normalized units		NS		NS		NS	–11.0	<0.0005	0.29
HF normalized units		NS		NS		NS	11.0	<0.0005	0.29

BMI, total cholesterol, and triglyceride were not independent explanatory variables. Smoking status was significantly related to TP and RMSSD (*P*=0.03, both). Only gender, BP group, age, and HDL cholesterol were included in R^2.
* Male=1, female=2.
† Normotensivecontrols (NT)=0; hypertensive patients (HT)=1.

groups (*r*=–0.65 and *r*=–0.61, respectively; *P*<0.01) but not in the female groups. In the female hypertensive group only, we found a significant correlation between systolic BP and BRS (*r*=–0.51; *P*<0.04).

Multiple Regression Analysis. Gender, age, and presence of hypertension were the only significant independent explanatory variables of BRS. BRS decreased with increasing age and was lower in female and hypertensive subjects than in men and normotensive subjects (Table 3).

Heart Rate Variability. Seventy–five 24–hour ECG recordings were analyzed. All had at least 18–hour recordings suitable for HRV analysis.

Differences Between Hypertensive and Normotensive Subjects. PNN50, RMSSD, TP, LF, and HF were lower in the hypertensive group than in the normotensive group. We did not find any significant differences in normalized units or LF/HF ratio between the hypertensive and normotensive subjects, although there was a nonsignificant tendency of higher LF/HF ratio in the hypertensive group (Table 4).

Gender Differences. Hypertensive women had higher HF normalized units and lower LF normalized units and LF/HF ratio than hypertensive men. Similar gender differences were found in the normotensive groups. The hypertensive women had significantly lower TP and LF

than the hypertensive men (Figures 2 and 3). There were significant differences between hypertensive and normotensive women in the same parameters as seen between the entire hypertensive and entire normotensive group (Figures 2 and 3). We did not find any significant differences between hypertensive and normotensive men in any of the HRV parameters.

Multiple Regression Analysis. Age, gender, HDL cholesterol, and presence of hypertension were the only significant independent explanatory variables of HRV numerical values, ie, the variability decreased with increasing age and was blunted in hypertensive subjects and women as opposed to normotensive subjects and men. HRV increased with increasing HDL concentrations. The normalized units of HF and LF were only related to HDL cholesterol, ie, the higher the HDL concentrations were, the lower were LF normalized units and the higher were HF normalized units. LF/HF ratio was related to both HDL and age, ie, LF/HF ratio decreased with increasing HDL and age (Table 3).

Hemoglobin, Hematocrit, Creatinine, and Blood Lipids.

Table 4. HRV in Normotensive vs Hypertensive Subjects

HRV Parameters	Normotensive	Hypertensive	*P*
n	34	41	
Mean R–R, ms	836 ± 16	802 ± 12	NS
SDNN, ms	151 ± 7	139 ± 5	NS
PNN50, %	9.8 ± 1.5	4.9 ± 0.6	0.003
RMSSD, ms	35.7 ± 3.0	28.7 ± 2.7	0.034
TP, ms^2	1797 ± 241	1224 ± 116	0.033
LF, ms^2	813 ± 115	550 ± 57	0.044
HF, ms^2	215 ± 38	141 ± 23	NS (0.055)
LF/HF ratio	4.75 ± 0.36	5.34 ± 0.48	NS
LF normalized units	80.2 ± 1.2	80.5 ± 1.4	NS
HF normalized units	19.8 ± 1.2	19.5 ± 1.4	NS

Data are mean ± SEM.

Differences Between Hypertensive and Normotensive Subjects. HDL cholesterol was higher in the hypertensive than in the normotensive group. We did not find any statistically significant differences in hematocrit, creatinine, total cholesterol, or triglycerides (Table 1).

Gender Differences. Hypertensive men had higher HDL than normotensive men. There were no statistically significant HDL differences between the 2 female groups. Female normotensive subjects had higher HDL ($P<0.0005$) than male normotensive subjects. Creatinine

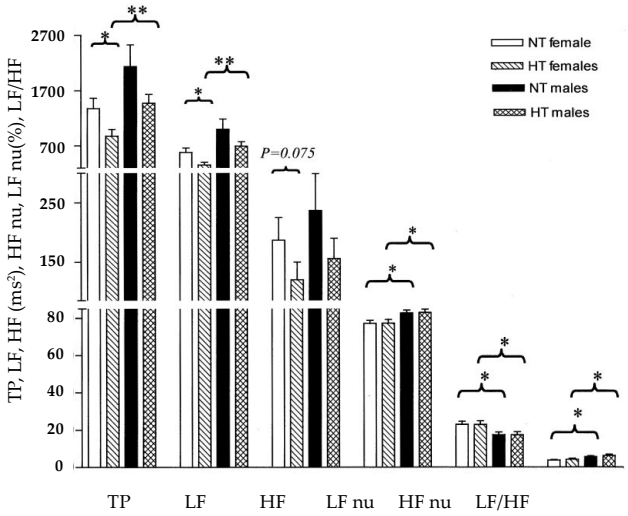

Figure 2. HRV frequency domain parameters in 41 hypertensive (HT) and 34 normotensive (NT) subjects. TP and LF were significant lower in hypertensive women than in normotensive women. HF was lower as well, but not at the level of significance. TP, LF, HF normalized units (nu), LF normalized units, and LF/HF ratio differed significantly between the male and female hypertensive groups. LF normalized units, HF normalized units, and LF/HF ratio differed significantly between the male and female normotensive groups. *P0.05; **P0.01.

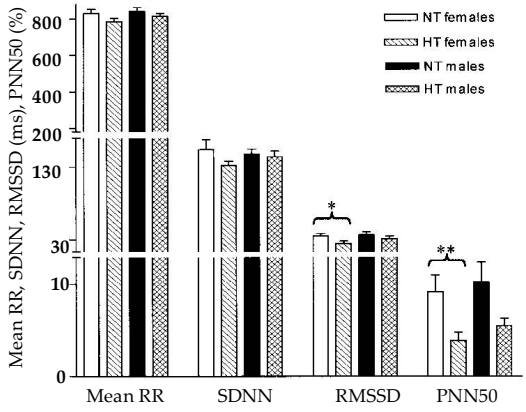

Figure 3. HRV time domain parameters in 41 hypertensive (HT) and 34 normotensive (NT) subjects. PNN50 and RMSSD were significantly lower in hypertensive women than in normotensive females. *P<0.05; **P<0.01.

and hematocrit was higher in the male group than in the female group ($P<0.001$). We did not find any gender differences in cholesterol and triglyceride (Table 2).

Discussion

The present study demonstrated significantly lower BRS in hypertensive subjects than in normotensive controls. Moreover, the reduction in BRS was most pronounced in the female group and did not reach statistical significance in men. BRS was also significantly reduced in hypertensive women compared with hypertensive men. Systolic BP correlated significantly with BRS in the female hypertensive group only.

In addition, we found significantly reduced TP, LF, PNN50, and RMSSD in hypertensive patients compared with normotensive controls. In our subgroup analysis these differences were only observed in the women and not in the men.

LF normalized units and LF/HF ratio were higher in men than in women in both BP groups. By multiple regression analysis, gender, age, and BP were independent determinants of BRS and HRV, TP, LF, HF, PNN50, and RMSSD. High HDL was associated with high values of HRV with the exception of LF normalized units and LF/HF ratio, which were negatively correlated. Thus, in the present study we have demonstrated substantial changes in the autonomic function in hypertensive patients. Moreover, autonomic dysfunction seems to play a more prominent role in female than in male hypertension.

The 4 groups were well matched with respect to gender, smoking, BMI, and age, making our subgroup analyses feasible without any confounding factors.

BRS was calculated with the transfer technique, which utilizes the spontaneous fluctuations in systolic BP and HR mainly induced by the respiration to estimate the BRS. It does not interfere with any cardiovascular control mechanisms[26] and correlates well with the phenylephrine ramp method in healthy[24] and hypertensive subjects.[7]

Our BRS results confirm the findings of reduced BRS in hypertensive patients.[6–10] BRS did not differ between normotensive men and women. This is in accordance with Laitinen et al,[14] who did not find any differ-

ence between healthy postmenopausal female subjects aged 60 to 77 years and male age–matched subjects.

Our finding of a substantial reduction of BRS, especially in female hypertension, warrants some comments. Rapid changes in HR following alterations in BP are mediated by the baroreceptor reflex arc, which is an important part of hemodynamic homeostasis. It has been suggested that hypertension is associated with a resetting of the reflex arc at a higher set point.[27] Female sex hormones may also be important in modeling female arteries. The compliance of the brachial artery is higher in women than in men.[28] Pregnant women have thinner arterial intima layer and thicker media layer than controls.[29] Estrogen therapy alone or in combination with simvastatin improves flow–mediated dilation of the brachial artery.[30] Interestingly, estrogen alone also increases HDL cholesterol concentrations.[30] These studies propose that female sex hormones model the arterial layers, which are crucial to the arterial BP buffer capacity and hence blood pressure variability and BRS. Furthermore, estrogen replacement therapy increases BRS in postmenopausal healthy women.[17] In our study all but 1 woman were postmenopausal, and BRS did not differ significantly between the male and the female normotensive groups. Arteriosclerotic plaques may mechanically cause arterial rigidity and consequently decrease BRS.[8] It is unlikely, however, that the women in our hypertensive group have more arteriosclerotic changes than their male counterparts. BRS is also lower in hypertensive subjects with insulin resistance than in hypertensive subjects with normal insulin tolerance.[6] Our study lacks data regarding insulin resistance, but there were no significant differences in BMI between the 4 groups, nor did any subjects suffer from diabetes. For these reasons we find it unlikely that different sex hormone concentrations, arteriosclerotic changes, or insulin resistance can explain our results. Moreover, the close relationship between BRS and BP only in hypertensive women supports the assumption that autonomic dysfunction may play a more important role in female hypertension.

The HRV differences between hypertensive and normotensive subjects demonstrated in the present study are in accordance with previous studies on HRV regarding the reduction in TP, HF, LF,[2,4–6] and PNN50.[2] We found a small and nonsignificant increase in the LF/HF ratio and LF normalized units in the hypertensive group compared with the normotensive group. This is in accordance with Pikkujamsa

et al[6] but not with Guzzetti et al,[3] who demonstrated significantly increased LF normalized units in the hypertensive group, and Huikuri et al,[5] who displayed decreased LF/HF ratio in the hypertensive group. Our subjects were examined twice, whereas Guzzetti et al only examined their subjects once. This may explain the diverging results. Most probably, the responses to the laboratory examination per se will differ between the first and second examinations.[31] The subjects in the study by Huikuri et al[5] were using vasoactive drugs at the time of the examination, which may have influenced the results. As demonstrated by other investigators[4,17,19] we found higher PNN50, LF/HF ratio, and LF normalized units in male normotensives than in female normotensives. We also confirmed the results of Singh et al[4] regarding PNN50, RMSSD, and LF/HF ratio in hypertensive men compared with hypertensive women, but, in contrast, we did not find any significant HRV discrepancies between the male hypertensive and normotensive groups. The probability of type II errors should be considered.

The reduction of overall HRV in hypertensive patients is more pronounced in women than in men. On the other hand, the relative HRV parameters, ie, normalized units and the LF/HF ratio, did not reveal any significant differences between the normotensive and hypertensive subjects in either the male or the female group. We can only speculate as to possible explanations of these results. One interpretation could be a generally more pronounced withdrawal of autonomic HR control in hypertensive women than in hypertensive men, even though the balance between the sympathetic and parasympathetic nervous system is similar. This assumption is further supported by the BRS results, which suggest less HR responsiveness to changes in systolic BP in hypertensive women compared with hypertensive men and normotensive subjects.

During the past decade, BRS has proven to be a powerful independent marker of increased risk for malignant cardiac arrhythmias and sudden death after myocardial infarction.[12,32] HRV measurements have also been investigated as predictors of cardiovascular morbidity. However the results have been diverging. While TP,[33] ultra low frequency power,[33] very low frequency power,[33] and SDNN[32] have proven to be independent markers of cardiovascular morbidity, the results regarding HF and LF have been less convincing.[33] We still lack a physiological understanding of the former HRV parameters, beyond that they reflect

a general variability.[23,33] Conversely, the physiological basis for the latter is better understood.[23]

On the basis of reports in patients with other kinds of cardiovascular diseases,[12,32,33] however, we might anticipate an association between low BRS and reduced HRV with cardiovascular morbidity in hypertensive subjects as well. On the basis of these considerations, our findings may imply that hypertensive women are more susceptible to cardiac events and arrhythmias than hypertensive men. No long–term studies, however, have been performed to investigate this possibility.

Acknowledgment

This study was supported by KNOLL, BASF Pharma, The Netherlands.

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